Date of Approval: June 18, 2004

FREEDOM OF INFORMATION SUMMARY

Original Abbreviated New Animal Drug Application

ANADA 200-297

Ivermectin Chewable Tablets
(ivermectin)

Antilarval

For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection.

Sponsor:

Phoenix Scientific, Inc.

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number:	ANADA 200-297
b. Sponsor:	Phoenix Scientific, Inc. 3915 South 48th St. Terrace St. Joseph, MO 64503 Drug Labeler Code: 059130
c. Established Name:	Ivermectin
d. Proprietary Name:	Ivermectin
e. Dosage Form:	Chewable tablet
f. How Supplied:	Each of 3 dosage strengths for dogs of different weights comes in packs of 12 chewable tablets with color coding on foil backing and carton.
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	Small tablets contain 68 mcg ivermectin; medium tablets contain 136 mcg ivermectin; large tablets contain 272 mcg ivermectin.
i. Route of Administration:	Oral
j. Species/Class:	Dogs
k. Recommended Dosage:	Administered orally at monthly intervals at the recommended minimum dose level of 6.0 mcg of ivermectin per kilogram (2.72 mcg/lb) of body weight. The recommended dosage schedule for prevention of canine heartworm disease is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Color Coding on Foil Backing and Carton
Up to 25 lb	1	68 mcg	Blue
26 to 50 lb	1	136 mcg	Green
51 to 100 lb	1	272 mcg	Brown

Give dogs over 100 lb the appropriate combination of these chewables. Recommended for use in dogs 6 weeks of age and older.

l. Pharmacological Category: Antilarval

m. Indications: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection.

n. Pioneer Product: HEARTGARD Chewables; ivermectin; NADA 140-886; Merial, Ltd.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA), an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

A Suitability Petition (98P-0159/CP1), requested by Phoenix Scientific, Inc., was granted to allow a generic copy of the pioneer's extruded chewable tablet with this compressed chewable tablet. The different oral dosage forms are similar and can be used interchangeably.

The sponsor has demonstrated *in vivo* bioequivalence via a blood-level bioequivalence study of the generic product to the pioneer product to support the safety and efficacy of the generic product against *Dirofilaria immitis* (see Section 2.A.). Palatability was also evaluated in dogs and the study is reported below in Section 2.B.

A. Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and pioneer formulations of ivermectin chewables. The dose was increased to three times (3 X) the recommended dose to achieve adequate blood levels for a determination of bioavailability. This is still far below the range where adverse reactions to the drug would be expected and is too low to affect the normal mechanisms associated with the metabolism and excretion of ivermectin in dogs.

Testing Facility: Liberty Research, Inc. (LRI)
Route 17C Box 107
Waverly, NY 14892-0107

Objective: The objective of this study was to determine the comparative blood-levels of Ivermectin (ivermectin) Chewable Tablets and HEARTGARD (ivermectin) Chewables in a 2 way crossover study in dogs.

Summary: Four male and four female Beagle dogs were randomly assigned to groups and used in a 2-way crossover study comparing Ivermectin Chewable Tablets to HEARTGARD Chewables. The dogs ranged in age from 4 to 7 years and weighed 25.6 to 28.6 pounds. The medications were administered one time during each treatment period crushed in food meatballs at a 3X dose to enable appropriate serum levels for a blood-level bioequivalence study. A 28 day washout was observed between treatments. Blood was collected at time 0, 1, 2, 3, 4, 5, 6, 8, 10, 16, and 24 hours, and 2, 3, 5, 7, 14, and 21 days post-treatment. Plasma samples were submitted to PPD Pharmaco, Inc., Middleton, WI for ivermectin analysis at the completion of the study.

Results: The area under the curve (AUC) was computed from time 0 until the last quantifiable concentration using the trapezoidal rule. The natural logarithm of AUC was computed and used as the variable for analysis, denoted by LAUC. The maximum concentration measured for all time periods (C_{max}) was determined and the natural logarithm of C_{max}, denoted by LCMAX, was computed and used as the variable for analysis.

The criteria for determining bioequivalence, as described in CVM's Bioequivalence Guidance, is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the log scale of AUC and C_{max} and then take the anti-log of the confidence limits minus 1 multiplied by 100. The resulting bounds should be between -20.00% and +25.00%. As seen in the table below both AUC and C_{max} fall within those bounds.

The variable T_{max} is permitted to be interpreted by clinical judgment. In this case, there is no reason to expect the difference in T_{max} will affect the efficacy of the drug, since both AUC and C_{max} are bioequivalent and the product is administered as a single dose. Therefore, the study objective to determine the bioequivalence of generic and pioneer ivermectin was achieved.

Variable	Pioneer Mean	Generic Mean	Lower Bound	Upper Bound
Time to Max. Concentration (hours)	6.375	4.125	NA[1]	NA[1]
Log_e(AUC)	5.635	5.649	-11.91%	16.76%
Log_e(CMAX)	2.374	2.396	-10.46%	16.86%

[1]Not Applicable

B. Palatability Study

Testing Facility: Liberty Research, Inc. (LRI)
Route 17C Box 107
Waverly, NY 14892-0107

Objective: The objective of this study was to evaluate the comparative palatability of Phoenix Scientific, Inc.'s (PSI) Ivermectin (ivermectin) Chewable Tablets to that of Merial, Ltd.'s HEARTGARD (ivermectin) Chewables.

Summary: The study was conducted to compare the palatability, measured as voluntary consumption, of generic (PSI) 136 mcg ivermectin chewable tablets and pioneer (Merial, Ltd.) 136 mcg ivermectin chewables (HEARTGARD Chewables) in the dog. The study involved three treatment groups, Ivermectin Chewable Tablets, HEARTGARD Chewables, and a flavored, unmedicated placebo treatment. Twelve dogs were used where every dog was presented each of the three treatments six times during the eighteen days of the study. Twelve series of treatment offerings were selected such that each animal had a unique series of treatment offerings. The series were selected such that four dogs received each treatment on each day of the study. Voluntary consumption was scored "yes" if the animal consumed and "no" if the animal did not consume the offered tablet during the offering time. The data collected on the placebo (treatment group C) was not used in the analyses.

Results: In this study, the generic product was voluntarily consumed 41 of the 72 offerings (56.9%) and the pioneer product was consumed in 45 of the 72 offerings (62.5%). The Table below (Table 2) provides a summary of the incidence of the results.

Table 2

Overall average percent consumption, based on six tablets presented to each of 12 animals.

Treatment	Average percent consumption
A (generic)	56.9%
B (pioneer)	62.5%
Note: All 12 dogs were offered six tablets of the generic treatment and six tablets of the pioneer treatment, for a total of 72 offerings of each type of tablet.	

A paired-t test using an arcsin square root transformation done on the difference in the percent consumption concluded that there was insufficient evidence to show that the generic and pioneer tablets were significantly different (p=.47).

3. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human warnings are provided on the package label as follows: "**Keep this and all drugs out of the reach of children.** In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans."

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that Ivermectin Chewable Tablets for Dogs, when used under the proposed conditions of use, is safe and effective for its labeled indications.

Safety and effectiveness for this generic animal drug, Ivermectin Chewable Tablets, were established by the demonstration of blood-level bioequivalence to the pioneer product, HEARTGARD Chewables, NADA 140-886, sponsored by Merial, Ltd. Palatability was also tested and found to be equivalent to that of the pioneer product.

5. ATTACHMENTS:

Facsimile generic labeling and currently approved pioneer labeling are attached as indicated below:

Generic Labeling:

Package Insert
Labels associated with foil packet, carton, and display tray:
12 chewable tablets- Dogs up to 25 lbs (blue).
12 chewable tablets- Dogs 26 to 59 lbs (green).
12 chewable tablets- Dogs 51 to 100 lbs (brown).

Pioneer Labeling:

Package Insert
Labels associated with foil packet and carton:
6 chewable tablets- Dogs up to 25 lbs (blue).
6 chewable tablets- Dogs 26 to 59 lbs (green).
6 chewable tablets- Dogs 51 to 100 lbs (brown).